Congenital cytomegalovirus (cCMV) among infants in U.S. neonatal intensive care units (NICU) during 2010-2020

Kelley Raines, MPH[1], Ashrita Rau, MPH[1], Reese Clark, MD[2], David Sugerman, MD MPH[1], Tatiana Lanzieri, MD MPH[1]

[1]National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, GA | [2]The Center for Research, Education, and Quality Improvement, Pediatrix Medical Group, Sunrise, FL

Objectives

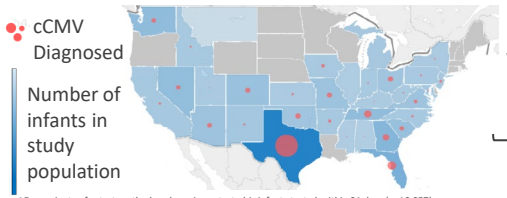
1. To describe clinical characteristics of infants tested and diagnosed for congenital cytomegalovirus (cCMV) in U.S. neonatal intensive care units (NICU) during 2010-2020
2. To examine the proportion of infants diagnosed with cCMV that met the CSTE cCMV confirmed case definition

Methods

- **Data source:** De-identified data derived from a proprietary electronic health record documentation system, Pediatrix® Medical Group Clinical DataWarehouse
- **Study population:** 840,988 infants admitted to 389 NICUs across 35 states during 2010-2020
- **cCMV diagnosis:** positive culture or PCR in urine, blood or cerebrospinal fluid (CSF) collected within 21 days of life
- **Analysis:**
  i. Measured the association between clinical signs and laboratory testing for CMV within 21 days using odds ratios (95% confidence intervals)
  ii. Among infants tested for CMV within 21 days, analyzed the frequency (by cCMV diagnosis) and positive predictive value (PPV) of clinical signs
  iii. Among infants diagnosed with cCMV, assessed the proportion who met the CSTE case definition for cCMV infection or cCMV disease based on CSTE evidence[d] and changes in proportions if additional clinical signs were included

Results

Figure 1: Map of infants with a cCMV diagnosis



Results

Table 1: Laboratory methods for CMV testing

Lab Methods	Tested for CMV	Positive for CMV[b]
Age of Test		
< 21 Days	10,057 (89.5%)	568 (5.6%)
22-42 Days	503 (4.5%)	77 (15.3%)
>42 Days	673 (6%)	252 (37.4%)
Test Method[a]		
PCR	3,250 (32.3%)	181 (5.6%)
Culture	6,807 (67.7%)	387 (5.7%)
Specimen Tested[ac]		
Urine	8,036 (79.9%)	527 (6.6%)
Blood	633 (6.3%)	29 (4.6%)
CSF	22 (0.2%)	4 (18.2%)
Saliva	1,366 (13.6%)	8 (0.6%)

Figure 2: Association of CMV Testing and clinical signs

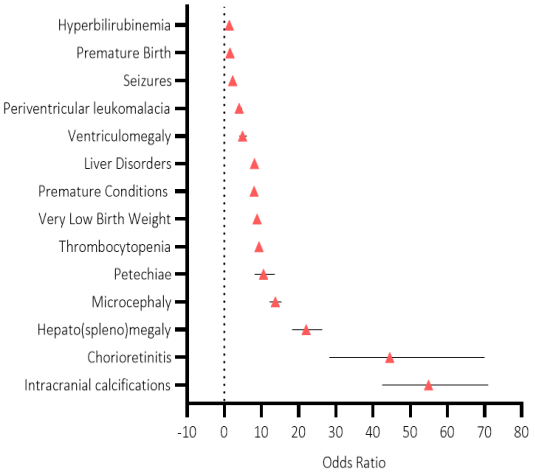


Figure 3: Frequency (by cCMV diagnosis) and PPV of clinical signs

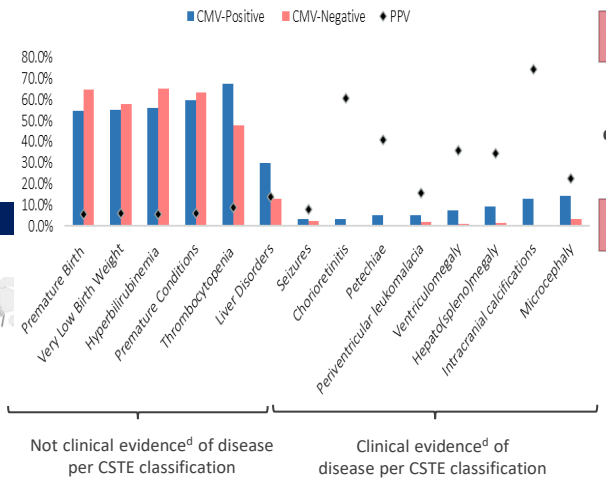


Figure 4: Case classification per CSTE case definition and with additional clinical signs

Classification per CSTE Case Definition

Infants with Confirmed **cCMV Infection**	Infants with Confirmed **cCMV Disease**
342 (61%)	218 (39%)

Including Additional Clinical Signs

Clinical Sign(s)	cCMV Disease n (%)
Liver Disorders	291 (52.0%)
Hyperbilirubinemia	417 (74.5%)
Thrombocytopenia	435 (77.7%)
Any of the Three	500 (89.3%)

Limitations

- Pediatrix® Data Warehouse houses data from only a subset of NICUs across the U.S. and the NICU population likely represents those with most severe co-morbidities, limiting generalizability
- Follow-up data not available beyond the NICU hospitalization to capture additional CMV testing, or late onset clinical signs included in the CSTE clinical evidence criteria (i.e., sensorineural hearing loss, cerebral palsy, and vision impairment)

Conclusions

- In this analysis of Pediatrix® data, only ~1% of infants hospitalized in NICUs in 35 US states were tested for CMV
- Among those tested, 90% of infants were tested for CMV within 21 days of life, by culture (68%) or PCR (32%), most commonly with urine (79%)
- Among ~10,000 infants tested for CMV within 21 days of life, 6% were positive (6.8 per 10,000)
  - Positivity rate for CMV increased to 15% for infants tested between 22-42 days, and 37% after 42 days of life
- Clinical signs with strongest association with CMV testing and highest PPV for cCMV diagnosis were intracranial calcifications, chorioretinitis, hepato(spleno)megaly, microcephaly, and petechiae
- Per CSTE criteria, 39% of infants with a cCMV diagnosis were classified as a case of confirmed cCMV disease
  - This proportion would increase to 52-78% with addition of liver disorders, hyperbilirubinemia or thrombocytopenia; however, these signs were also very common in infants with a negative test for CMV, resulting in low PPV
- Future work could examine the association of neonatal clinical signs with long-term sequelae

Contact Information:
Kelley Raines |
KRaines@cdc.gov

[a] Denominator for test method and specimen tested is infants tested within 21 days (n=10,057)
[b] Row percent reported
[c] A minority of infants were tested twice, with urine and blood or urine and CSF, these were included in the urine category
[d] CSTE clinical evidence of disease: a) An infant with at least one of the following clinical signs during the neonatal period: Hepatomegaly, Splenomegaly, Petechial rash or purpura; b) A child aged 6 years or younger with one or more of the following permanent conditions: Microcephaly, Brain imaging abnormalities consistent with cCMV, Sensorineural hearing loss, Seizures, Cerebral palsy, Chorioretinitis, Vision impairment, resulting from conditions consistent with cCMV